REMARKS/ ARGUMENTS

Applicant has carefully studied the non-final Examiner's Action mailed January 13, 2009, having a shortened statutory period for response set to expire April 13, 2009. The amendment appearing above and these explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Interview Summary

Applicant would like to thank Examiner Jagoe for conducting the interview on April 1, 2009. During the interview, the enablement rejection was discussed, specifically address the breadth of the side effects being treated by the present invention. A typographical error was also discussed on page Page 6 of the non-final Office, wherein anti-neoplastic agents should read anti-inflammatory agents.

The rejection under 35 U.S.C. § 103 was also discussed. Applicant noted that the references do not address the co-treatment of anti-inflammatory agent and MAO inhibitor. Examiner Jagoe expressed concerns related to the depletion of endogenous mucous secretion as a hallmark of anti-inflammatory drug treatment. It was also discussed that anti-inflammatory drugs inhibit prostaglandin, thereby reducing the mucous layer, which may be treated with misoprostol.

Claim Rejections - 35 U.S.C. § 112

Office has rejected claims 1-5, 7, 17, and 20 under 35 U.S.C § 112, first paragraph, for failing to enable the claimed invention. Applicant has amended the claims to claim "preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs and enhancing the beneficial effects of anti-inflammatory drugs[.]"

To determine whether a disclosure adequately enables an invention, a series of factors have been established, including the breadth of claims, nature of the invention, state of prior art, relative skill in the art, predictability in the art, the amount of direction or guidance, presence of working examples, and amount of experimentation needed.[1] 35 U.S.C. § 112 is satisfied if "the specification contains within it *a connotation* of how to use" the invention or the use is known in the art.[2]

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[1] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).
[2] MPEP 2164.01(c). (Emphasis added).

Breadth of Claims

The Office contends the claims are overbroad, as the claims cover preventing gastrointestinal side effects of anti-inflammatory drugs.[3] Applicant has amended claim 1 to provide "preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs [.]" Claim 1 is thus limited to a very specific effect of the anti-inflammatory drugs.

Antiinflammatory drug effects are generally mediated through cyclooxygenase (COX) enzyme inhibition,[4] thereby reducing eicosanoid and prostaglandin synthesis.[5] Nonselective COX inhibition causes adverse effects, including gastrointestinal (GI) problems like gastroduodenal ulcers and gastrointestinal bleeding.[6] Further, anti-inflammatory treatment results in neutrophil adhesion, mucosal blood flow reduction, mucous diminishment, and free radical production.[7] Because anti-inflammatory drugs typically rely on the same pathway, at least partly, the side effects of anti-inflammatory drugs may be prevented and treated by targeting such common pathways. Antiinflammatory drug effects are reversed by MAO inhibitors, such as deprenyl, through effects including free radical scavenging, antioxidant properties, stimulation of antioxidant enzyme expression, endothelial protection, vasodilation, enhanced blood flow, and stimulation of nitrogen oxide synthase.[8] The specification shows administering an MAO-B inhibitor prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reverses gastrointestinal lesions by one week pretreatment.[9]

Nature of the Invention, State of the Art and Predictability

The Office found the nature of the invention "relates to a method of 'preventing, reducing and reversing the toxic side effects' caused by anti-inflammatory drugs with a MAO

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[3] Page 5 of the non-final Office Action, dated Jan. 13, 2009.
[4] Page 2 of the Application; J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, "Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme," Proc. Nat. Acad. Sci., 1992, 89, 3917-3921, page 3919, column 2.
[5] Page 2 of the Application; J. Masferrer, K. Seibert, B. Zweifel, P. Needleman, "Endogenous Glucocorticoids Regulate an Inducible Cyclooxygenase Enzyme," Proc. Nat. Acad. Sci., 1992, 89, 3917-3921, page 3919, column 2.; Solomon, D., "Recommendations for use of selective and nonselective nonsteroidal anti-inflammatory drugs: an American college of rheumatology white paper", Arthritis Rheum. 2008 Aug 15;59(8):1058-73, page 1059, column 1.
[6] Unknown author, "Balancing Cardiovascular Rishs and Gastrointestinal Outcomes in NSAID Users; A Report from a Symposium held During the American College of Gastroenterology 71st Annual Meeting and Postgraduate Course," Gastroent. & Hepat., Mar. 2007, 3:3, 4-13, page 4, column 1.
[7] Page 4 of the Application.
[8] Pages 17-18 of the Application.
[9] Example 5, pages 22-23; table 3, page 25 of the Application.

inhibitor."[10] Though the relative skill in the art is high, that of an M.D. or Ph.D., the Office concluded that this is outweighed by the unpredictability in the art.[11]

The specification provides examples of MAO inhibitors preventing anti-inflammatory drug side effect damage. For example, administering an MAO-B inhibitor prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reversed gastrointestinal lesions by one week pretreatment.[12] In similar experiments conducted over 7 days, pretreatment with L-deprenyl or propargylamine prevented formation of gastric lesions and reversed lesions.[13] Administering 5 mg/kg deprenyl prior to a NSAID result in inhibition of leukocyte activation and adhesion,[14] and administering 0.5 mg/ kg propargylamine (MAO inhibitor from example 1) prior to a NSAID provided protection to gastrointestinal mucous after one pretreatment and reversed gastrointestinal lesions by one week pretreatment.[15] The use of MAO inhibitors therefore shows a reduction in adverse effects of anti-inflammatory drugs, namely neutrophil adhesion, mucosal blood flow reduction, mucous diminishment, and free radical production.[16]

The Office notes that the Merck Manual states that "[b]y inhibiting prostaglandin production via blockage of the enzyme cyclooxygenase (COX), NSAIDs reduce gastric blood flow, reduce mucus and HCO_3 secretion, and decrease cell repair and replication."[17] Applicant respectfully points out that examples within the specification disclose that MAO inhibitors reverse these effects.[18]

Amount of Direction or Guidance/ Working examples

The Office states that "[t]he specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to reduce all of the various side effects of anti-inflammatory drugs."[19] The

[10] Page 4 of the non-final Office Action, dated Jan. 13, 2009.
[11] *Id.*
[12] Example 5, pages 22-23; table 3, page 25 of the Application.
[13] *Id.*
[14] Example 3, pages 21-22 of the Application.
[15] Example 5, pages 22-23; table 3, page 25 of the Application.
[16] Page 4 of the Application.
[17] Page 5 of the Application.
[18] Pages 17-18; 22-23of the Application.
[19] Page 6 of the non-final Office Action, dated Jan. 13, 2009.

Office contends the results only show l-deprenyl prevented aspirin- or indomethacin-induced ulceration for 7 days.[20]

The Office also found the results do not "evidence that the claimed combination has any effect in preventing long term side effects."[21] Applicant submits that the claims provide for "preventing, reducing and reversing the gastrointestinal ulceration effects[,]" which are shown in Example 5 of the specification. The specification provides that NSAID gastropathology is a result of gastric microcirulation[22] and that MAO inhibitors may be administered at 0.1 to 10 times the NSAID dose of 0.1-500 mg/kg.[23] L-deprenyl shows a reduction in gastric lesion damage at 100 mg/kg and at 200 mg/kg; 21-40% and 1-20% of lesions in mice treated only with anti-inflammatory, respectively.[24, 25] The specification also includes working examples of the invention in reducing gastric ulceration, illustrating that the administration of MAO inhibitor provides a protective effect for cells.[26]

The application also discloses MAO inhibitor tests on C-reactive protein, which is elevated in obesity and diabetes and a possible side effect of hormone therapy.[27] Blood samples were taken from human subjects, followed by administration of L-deprenyl.[28] After seven days, blood CRP levels were reduced 30% in L-deprenyl-treated individuals.[29]

Not every embodiment or procedure to practice the invention need be disclosed for the invention to be enabled.[30] The application discloses that MAO inhibitors L-deprenyl and propargylamine effectively prevent formation of gastric lesions and reverse lesion progression during prolonged treatment, as seen in table 3.[31] The claims do not require all side effects of each drug be prevented, but rather for enablement the invention must prevent or treat at least one side effect of the drugs. L-deprenyl and propargylamine treatment is shown effective in preventing and reducing NSAID side effects. SAIDs act through the same pathway as NSAIDs,

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[20] *Id.*
[21] Page 6 of the non-final Office Action, dated Jan. 13, 2009.
[22] Page 4 of the Application.
[23] Page 19 of the Application.
[24] Page 25, table 3 of the Application.
[25] Example 5, pages 22-23; table 3, page 25 of the Application.
[26] Page 25, table 3 of the Application (Providing lesion reduction at provided dosages for L-deprenyl and propargyline).
[27] *Id.* at page 24.
[28] *Id.*
[29] *Id.*
[30] MPEP2164.08
[31] *Id.* at page 23; table 3.

by inhibiting COX, to produce an anti-inflammatory effect. Though NSAIDs and SAIDs have different side effects, both anti-inflammatory treatments utilize COX-dependent pathways. As such, the application discloses at least one example of preventing the side effects of NSAIDs and SAIDs. Therefore, NSAIDs and SAIDs may be effectively treated by compounds that target such similar pathways and the claims are consistent with the scope of the disclosure.

A specification does not require working examples, but may utilize prophetic examples to describe the invention based on "predicted results."[32] The specification does include working examples of the invention in reducing platelet activation and reducing gastric ulceration.[33] Applicant respectfully submits that the administration of an MAO inhibitor was found to (1) prevent the occurrence of ulceration following anti-inflammatory treatment;[34] and (2) reverse the ulceration cause by previous anti-inflammatory treatment.[35] Cardiovascular events, caused by anti-inflammatory treatment, develop due to the prothrombic activity of the drugs, causing platelet coagulation and resulting in cardiovascular events like congestive heart failure, stroke, vascular death, and myocardial infarction.[36] Leukocyte activation and adhesion is known in the art,[37] and pretreatment of L-deprenyl (5 mg/kg) inhibited leukocyte activation induced by TNF-α,[38] thereby preventing cardiovascular events caused by anti-inflammatory drugs. Additionally, the specification discloses L-deprenyl and propargylamine reduces and prevents gastric lesions,[39] commonly caused by anti-inflammatory drug treatment. Thus, the specification illustrates that the treatment of an MAO inhibitor effectively prevents, reduces, and reverses the effects of anti-inflammatory drugs.

Amount of Experimentation Required

Due to the unpredictability in the art, the Office stated a "skilled artisan would not accept the assertion that the instantly claimed combination could be predictably used to lower the side effects caused by antineoplastic [antiinflammatory] agents as inferred in the claims and

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[32] MPEP 2164.02. Citing *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).
[33] Examples 3 and 5, pages 21-23 of the Application.
[34] See, page 22-23 of the Application (for example, "Pretreatment with l-deprenyl provided protection against the NSAID induced gastric lesion.")
[35] See, page 22-23 of the Application (for example, "The gastric lesions were also reversed by daily administration of l-deprenyl for 7 days.")
[36] *Id.* at page 5-6.
[37] See, T. Thomas, J. Rhodin, L. Clark, A. Garces, "Progestin Initiate Adverse Events of Menopausal Estrogen Therapy," Climacteric, Dec. 2003; 6(4):293-301.
[38] Example 3, page 21 of the Application.
[39] Example 5, page 23; table 3, page 25 of the Application.

contemplated by the specification."[40] Further, the Office found "Applicants have presented a general idea that because aspirin or indomethacin administered with l-deprenyl is not acutely toxic to mice then this combination must, *a priori*, be useful to 'prevent toxic gastrointestinal side effects'[.]"[41] Applicant respectfully submits that the administration of an MAO inhibitor was found to (1) prevent the occurrence of ulceration following anti-inflammatory treatment;[42] and (2) reverse the ulceration cause by previous anti-inflammatory treatment.[43]

"Enablement is not precluded by the necessity for some experimentation *such as routine screening*."[44] Varying the timing for treatment administration and/or the dosage of anti-inflammatory and MAO inhibitor is essentially a drug screening process. According to *Wands*, screening is within the routine practice of the medicinal and scientific arts.[45] Based on the prior work performed in the art, the level of skill in the art, and the disclosure, the invention is adequately described for prevention, reduction, and reversion of the side effects of anti-inflammatory drugs.

35 U.S.C. § 112 is satisfied if "the specification contains within it *a connotation* of how to use" the invention or the use is known in the art.[46] Office bears the initial burden to show the specification does not enable the claimed invention. The medicinal and scientific arts are highly skilled arts, as discussed *supra*. The specification provides guidance as to the timing and dosage of MAO inhibitor, as refers to the prior art (PDR) for calculations on patient dosages. The specification does include working examples of the invention in gastrointestinal ulceration prevention and reduction/ reversion, as well as prevention of cardiovascular events. As such, based on the prior art, skill of the ordinary artisan, and disclosure, the invention is adequately described to allow a skilled artisan to use the invention for treatment for preventing, reducing and reversing the toxic effects of anti-inflammatory drugs. The *Wands* factors indicate the invention may be performed without undue experimentation, as discussed *supra*. Accordingly, it is respectfully requested that the rejection of claims 1-5, 7, and 20 be withdrawn by the Office.

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[40] Page 6 of the non-final Office Action, dated Jan. 13, 2009.
[41] Page 7 of the non-final Office Action, dated Jan. 13, 2009.
[42] See, page 22-23 of the Application (for example, "Pretreatment with l-deprenyl provided protection against the NSAID induced gastric lesion.")
[43] See, page 22-23 of the Application (for example, "The gastric lesions were also reversed by daily administration of l-deprenyl for 7 days.")
[44] *In re Wands*, 858 F.2d at 736-737. (Emphasis added).
[45] See generally, *In re Wands*, 858 F.2d at 739.
[46] MPEP 2164.01(c). (Emphasis added).

Claim Rejections - 35 U.S.C. § 112

The Office has rejected claims 1-5, 7, 17, and 20 under 35 U.S.C § 112, second paragraph.

Claim 2 stands rejected for omitting essential structural relationships, specifically for failure to define "statins".[47] Applicant submits that the art and specification may be used to define terms in the claims.[48] As provided in the specification, "statins are compounds used to lower lipid levels and accord protection from cardiovascular disease."[49] Thus, the term "statins" may be used only on compounds that are known as "statins" and which "lower lipid levels and accord protection from cardiovascular disease". As such, Applicant respectfully submits that the term "statins" does provide definition.

Claims 1 and 2 are rejected as "NSAID", "COX", and "MAO inhibitor" does not provide the full name of the compound. Applicant submits that the specification does describe that NSAID is a non-steroidal anti-inflammatory drug,[50] COX is cyclooxygenase,[51] and MAO stands for monoamine oxidase.[52] However, Applicant has amended the claims to provide the full name, followed by the abbreviation.

Claim 7

Applicant gratefully acknowledges the concerns enunciated by Examiner Jagoe and has amended the claims to address the Examiner. Accordingly, Applicant respectfully requests withdraw of the 35 U.S.C § 112, second paragraph rejection of claims 1-5, 7, 17, and 20.

Claim Rejections - 35 U.S.C. § 103

Claims 1-5, 7, 17, and 20 stand rejected under 35 U.S.C. § 103(a) in view of *Glavin, et al.* (Neurosci. Ltrs., 1986) and *Lianping, et al.* (Dig. Disease Sci., 1990). The Office found that *Glavin, et al.* teaches an association between duodenal ulcer occurrence and dopamine deficiency.[53] The Office noted disorders with excessive dopamine activity rarely associate with duodenal ulcers (pathology), and pretreatment with L-deprenyl prevented ulcers in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated rats.[54] The Office further found *Lianping, et*

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[47] Page 8 of the non-final Office Action, dated Jan. 13, 2009.
[48] See, MPEP 2111.01; MPEP 2111 ("broadest reasonable interpretation that those skilled in the art would reach").
[49] Page 7 of the Application.
[50] Pages 1-2 of the Application.
[51] Page 2 of the Application.
[52] Page 8 of the Application.
[53] Page 10 of the non-final Office Action, dated Jan. 13, 2009.
[54] *Id.*

al. "teach[es] MAO inhibitors reduced restraint stress-induced gastric ulceration by inhibition of gastrin release (page 61) resulting in a protection of the gastric mucosa."[55] Though neither *Glavin, et al.*[56] nor *Lianping, et al.*[57] "teach a method of preventing, reducing, and reversing the toxic effects of anti-inflammatory drugs[,]" the Office found it was obvious to employ MAO inhibitors to prevent the toxic effects of anti-inflammatory agents because *Glavin, et al.* teaches l-deprenyl prevents ulceration in dopamine depleted rats and *Lianping, et al.* teaches MAO inhibition protects from stress-induced gastric ulceration, thus disclosing protective gastrointestinal effects.[58] In support of the obviousness finding, the Office found "[o]ne of ordinary skill in the art would have been capable of applying this known technique to a known method that was ready for improvement and the *results would have been predictable* to one of ordinary skill in the art."[59] Applicant submits that the combination fails to obviate the claimed invention because (1) the combination of references fail to disclose the claimed invention; and (2) the Office has not propounded a rationale support for the finding of obviousness.

The combination of *Glavin, et al.* and *Lianping, et al.* fail to obviate the claimed invention as the references do not disclose the elements claimed. Claim 1, as amended provides:

> A method of preventing, reducing and reversing the gastrointestinal ulceration effects of anti-inflammatory drugs and enhancing the beneficial effects of anti-inflammatory drugs, comprising:
>
> administering to a subject an effective amount of MAO inhibitor;
>
> wherein the anti-inflammatory drug and MAO inhibitor are chemically linked, physically mixed or administered separately.

"Ascertaining the differences between the claimed invention and the prior art requires interpreting the claim language … and considering both the invention and the prior art as a whole.[60] As noted by the Office, *Glavin, et al.* and *Lianping, et al.* focus on dopamine levels.[61]

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[55] *Id.*
[56] *Id.* at page 10.
[57] *Id.* at page 11.
[58] *Id.*
[59] Page 11 of the non-final Office Action, dated Jan. 13, 2009 (emphasis added).
[60] MPEP 2141(II)(B).
[61] Page 10 of the non-final Office Action, dated Jan. 13, 2009. See also, Lianping Xing, J. Seaton, G. Kauffman, "Monoamine Oxidase B Inhibition Reduces Gastric Mucosal Blood Flow, Basal Acid Secretion, and Cold Water Restrain-Induced Gastric Mucosal Injury in Rats," Digestive Dis. And Sci., Jan. 1990; 35(1):61-65, page 61, abstract (DA and NE concentrations in nucleus accumbens is associated with restraint-induced mucosal injury), page 64, column 2 (data indicates central inhibition of MAO-B increases DA and NE concentrations, and indicates central DA and NE are involved in gastric mucosal control); G. Glavin, A. Dugani, C. Pinsky, "L-Deprenyl Attenuates Stress Ulcer Formation in Rats," Neurosci. Ltrs. 1986; 70:379-381, page 380-381.

All the limitations of a claim must be considered when weighing the differences between the claimed invention and the prior art in determining the obviousness of a process or method claim.[62] However, the references fail to discuss anti-inflammatory agents or indicate any relevance to anti-inflammatory agents. Because the references do not address the use of MAO inhibitors with anti-inflammatory drugs, not all the limitations of the claim were considered in evaluating the nonobviousness of the claimed invention. Obviousness must be determined by comparing the differences between the claimed invention and prior art.[63] In *In re Hirao*, a three step process was determined nonobviousness over a two step process teaching a similar method, as the prior art, when compared to the claimed invention as a whole, did not obviate the invention.[64] Similarly, Applicant submits the failure of the references to disclose the use of anti-inflammatory drugs is fatal to the obviousness determination.

A *prima facie* case of obviousness has not been established because the Office has not propounded a rationale support. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious"[65] The Office stated that ""[o]ne of ordinary skill in the art would have been capable of applying this known technique to a known method that was ready for improvement and the *results would have been predictable* to one of ordinary skill in the art."[66] However, Applicant respectfully points out that the Office found that there is a "lack of significant guidance from the … prior art with regard to the actual prevention of side effects of anti-inflammatories with the claimed compounds mak[ing] practicing the claimed invention *unpredictable*."[67]

Applicant submits that the high level of unpredictability found in the art, under 35 U.S.C. 112, which prevents the invention from being enabled, also precludes one skilled in the art from predictably creating the invention from the prior art. As noted in MPEP 2164.01, the enablement test relies on what "one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art[.]"[68] However, it is paradoxical that the invention is not enabled by the specification and prior art, based in part on

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[62] MPEP 2116.01 (citing also to MPEP 2143.04)
[63] MPEP 2141.02(I).
[64] *Id.* (citing *In re Hirao*, 535 F.2d 67, 190 U.S.P.Q. 15 (CCPA 1976)).
[65] MPEP 2142.
[66] Page 11 of the non-final Office Action, dated Jan. 13, 2009 (emphasis added).
[67] Page 6 of the non-final Office Action, dated Jan. 10, 2008. See also, Page 4 of the non-final Office Action, dated Jan. 13, 2009 (finding the level of unpredictability in the art outweighs the high level of skill).
[68] See also, 2163(II)(A)(2).

the unpredictability of the art, while the predictability in the art obviates the invention. Because the prior art is unpredictable, Applicant submits that it would not be predictable to combine *Glavin, et al.* and *Lianping, et al.* As such, the references fail to obviate the claimed invention.

Applicant also submits that prostaglandins and glucocorticoids are key molecules in inflammatory response.[69] Cyclooxygenase isoforms COX-1 and COX-2 are responsible for the "synthesis of prostaglandins from arachidonic acid."[70] COX-2 selective NSAIDs appear to indicate that COX-1 inhibition is results in upper GI mucosa side effects,[71] however some in vivo models also suggest that concurrent COX-1 and COX-2 inhibition is required for gastric ulceration.[72] "[P]atients with a history of NSAID use, [exhibit] gastric and duodenal ulcers[.]"[73] Current prevention involve "co-therapy with a PPI, high dose (2x) histamine-2-receptor antagonist (H_2RA), or the synthetic prostaglandin E1 analog, misoprostol" or use of COX-2 selective inhibitors.[74] Studies show that acid-suppressant drugs, such as H_2RAs, "delayed healing of ulcers … in patients who … continued to take NSAIDs."[75]

NSAID-associated prostaglandin depletion has been treated using prostaglandin analogue Misoprostol.[76] There are concerns with tolerability, compliance and dose-related side effects, limiting the usefulness of Misoprostol.[77] Further, the effectiveness of Misoprostol is limited, with proton pump inhibitors exhibiting significantly better protection.[78]

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[69] Masferrer, J., et al., "Endogenous glucocorticoids regulate an inducible cyclooxygenase enzyme", Proc. Nat'l Acad. Sci. U.S.A. 1992 May 1;89(9):3917-21, page 3917, column 1.
[70] Solomon, D., "Recommendations for use of selective and nonselective nonsteroidal anti-inflammatory drugs: an American college of rheumatology white paper", Arthritis Rheum. 2008 Aug 15;59(8):1058-73, page 1059, column 1.
[71] Solomon, D., Arthritis Rheum. 2008 Aug 15;59(8):1058-73, page 1059, column 1.
[72] Balancing Cardiovascular Risks and Gastrointestinal Outcomes in NSAID Users, Gastroent. & Hepta. 2007 Mar; 3(3)S13:4-13, page 5, column 2.
[73] Lanza, F., et al., "Guidelines for prevention of NSAID-related ulcer complications", Am. J. Gastroenterol. 2009 Mar;104(3):728-38. Epub 2009 Feb 24, page 729, column 1.
[74] *Id.*at page 730, column 2.
[75] Yajima, H., et al., Up-to-date information on gastric mucosal lesions from long-term NSAID therapy in orthopedic outpatients: a study using logistic regression analysis, J. Orthop. Sci. 2007 Jul;12(4):341-6. Epub 2007 Aug 2, page 345, column 1.
[76] Balancing Cardiovascular Risks and Gastrointestinal Outcomes in NSAID Users, Gastroent. & Hepta. 2007 Mar; 3(3)S13:4-13, page 8, columns 1-2.
[77] Balancing Cardiovascular Risks and Gastrointestinal Outcomes in NSAID Users, Gastroent. & Hepta. 2007 Mar; 3(3)S13:4-13, page 8, column 2 (see Misoprostol and Proton Pump Inhibitors sections).
[78] Balancing Cardiovascular Risks and Gastrointestinal Outcomes in NSAID Users, Gastroent. & Hepta. 2007 Mar; 3(3)S13:4-13, page 8, column 2.

The present invention provides cytoprotection to GI mucosa[79] through MAO inhibition by effects such as free radical scavenging, antioxidant properties, stimulation of antioxidant enzyme expression, endothelial protection, vasodilation, enhanced blood flow, and stimulation of nitrogen oxide synthase.[80] Conversely, studies of existing cytoprotective anti-ulcer drugs have shown the drugs are "ineffective in preventing ulceration."[81]

The combination of *Glavin, et al.* and *Lianping, et al.* fail to obviate the present invention because the combined references fail to disclose the elements of the claimed invention. Further, a *prima facie* case of obviousness has not been established as the rationale used to support the obviousness finding relies on the predictability in the art, which the Office has also found to be lacking. Accordingly, Applicant respectfully requests the 35 U.S.C. § 103(a) rejection of claims 1-5, 7, 17 and 20 be withdrawn.

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

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Dated: April 13, 2009
Customer No. 21,901

[79] See, page 18 of the Application ("the cytoprotective effect of MAO inhibitors in preventing and/or reversing the NSAID toxicity may be mediated by a combination of several cytoprotective actions[.]")
[80] Pages 17-18 of the Application.
[81] Nakashima, S., et al., Usefulness of anti-ulcer drugs for the prevention and treatment of peptic ulcers induced by low doses of aspirin, World J. Gastroenterol. 2009 Feb 14;15(6):727-31, page 1, column 2.

CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

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Lauren Reeves